Oral Oncology 97 (2019) 37–43

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Comparison of GP and TPF induction chemotherapy for locally advanced nasopharyngeal carcinoma

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ARTICLE INFO

Keywords:
Nasopharyngeal carcinoma
Induction chemotherapy
GP regimen
TPF regimen

ABSTRACT

Objectives: This study aims to compare two induction chemotherapy regimens, TPF and GP, for patients with locally advanced nasopharyngeal carcinoma (NPC).

Materials and methods: We analyzed patients with newly diagnosed stage III-IVA NPC (excluding T3/T4N0, AJCC) between December 2010 and May 2015 who were treated with TPF or GP induction chemotherapy (IC) followed with concurrent chemoradiotherapy (CCRT) and those treated with CCRT alone. Treatment compliance, survival outcomes and grade 3–4 side effects were compared among these three groups.

Results: A total of 189 patients were eligible for this study, with 87 (46.0%), 71 (37.6%) and 31 (16.4%) in the TPF, GP and CCRT alone groups. All patients were followed for 3 years. There was no difference in the 3-year survival rate between GP- and TPF-treated patients. Disease-free survival (DFS) and overall survival (OS) were significantly improved in both IC groups compared with those in the CCRT alone group. Multivariable analysis suggested that patients with N3 had a higher risk of distant metastasis than those with N1-2. GP is not inferior to TPF regardless of different N categories. There were significant more grade 3–4 treatment-related toxicity in TPF group than in GP group.

Conclusion: Our study found that in locally advanced NPC, the GP induction chemotherapy regimen is equivalent to TPF in treatment outcomes, but with significant less grade 3–4 acute toxicity. Further studies are needed to validate our findings.

Introduction

Nasopharyngeal carcinoma (NPC) has a unique endemic distribution around the world, with the highest incident rate in southern China, southeast Asia, and northern Africa [1]. Approximately 70% of newly diagnosed NPC patients present with locoregionally advanced disease [2]. Radiotherapy (RT) is the primary curative treatment modality for nasopharyngeal carcinoma because of its special anatomical location and high sensitivity to radiation. After application of intensity-modulated radiotherapy (IMRT) and a combination of chemoradiation, the local control rate of locoregionally advanced NPC (LA-NPC) has increased. Distant metastasis remains the major pattern of failure [3] and is affected by different combinations of radiotherapy and chemotherapy. Present modalities of chemoradiotherapy include concurrent chemoradiation (CCRT), induction chemotherapy (IC), and adjuvant chemotherapy (AC). The value of CCRT has been shown by the randomized Intergroup 0099 study, several subsequent clinical trials [4–7], and several meta-analyses [8–10]. Other studies have found that adjuvant chemotherapy, given after radiotherapy, did not benefit patients with advanced NPC [11–14]. Compared with AC, induction chemotherapy (IC) is better tolerated and thus permits a high drug concentration to improve the survival rate of patients with locally advanced nasopharyngeal carcinoma. Micrometastatic disease may be eradicated by IC early. Increasing evidence has already shown the benefit of adding IC to CCRT [15–18]. The treatment modality of IC followed by CCRT is widely used for locally advanced nasopharyngeal carcinoma in epidemic areas in China. However, the optimal IC regimens remain unclear.

Compared with other IC regimens, the regimens of TP (docetaxel, cisplatin), PF (cisplatin, fluorouracil) or TPF (docetaxel, cisplatin,

Abbreviations: TPF, docetaxel, cisplatin and fluorouracil; GP, cisplatin plus gemcitabine; CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; DFS, disease-free survival; OS, overall survival

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https://doi.org/10.1016/j.oraloncology.2019.08.001
Received 24 January 2019; Received in revised form 1 August 2019; Accepted 3 August 2019
Available online 08 August 2019

fluorouracil) are considered the most effective combinations [19–21]. The TPF regimen has been further proven to be superior to the TP and PF regimens; however, the incidence of treatment side effects is higher. GP (gemcitabine, cisplatin) as a new chemotherapy regimen is shown to be more effective and tolerable for metastatic and recurrent NPC [22,23] and has already shown promising efficacy and mild toxic events in some studies [24–28]. This study aims to compare the efficacy of the induction chemotherapy regimens GP and TPF and to explore the optimal regimen of induction chemotherapy for locally advanced nasopharyngeal carcinoma.

Materials and methods

Eligibility criteria

We collected data from patients with NPC who were treated at West China Hospital of Sichuan University from December 2010 to June 2015. The inclusion criteria were as follows: (a) patients with histologically confirmed stage III-IV (except T3–4N0; 7th Union for International Cancer Control and American Joint Committee on Cancer) (UICC/AJCC); (b) patients aged at least 18 years old; (c) patients with Karnofsky performance status scores ≥ 70; (c) patients with no evidence of other malignancies; (d) patients treated with induction chemotherapy (GP or TPF) or only concurrent chemotherapy; (e) patients treated with single-agent cisplatin as the regimen of concurrent chemotherapy; (f) patients treated with IMRT as the radiotherapy technique.

The data included physical examination of the head and neck, nasopharyngeal fiberscope examination, magnetic resonance imaging (MRI) scans of the head and neck, chest radiography or computed tomography (CT), whole body bone scans, abdominal sonography, and blood profiles including pretreatment levels of lactate dehydrogenase (LDH), copies of plasma Epstein-Barr virus deoxyribonucleic acid (EBV DNA) before and after treatment, and leukocyte, erythrocyte, platelet, and neutrophilic granulocyte counts. Based on our previous study, we set the cut-off value of pretreatment copies of EBV DNA as 10^3 copies/ml [35]. Smoking or drinking history was also reviewed and analyzed. All patients were restaged according to the 8th edition of the UICC/AJCC manual. This study was approved by the ethics committee of West China Hospital, Sichuan University, and informed consent was waived.

Radiotherapy

All patients were treated with IMRT with 6 MV photon beginning 21 days after the start of the last cycle of IC. Simulation CT was performed with contiguous slices 3–5 mm thick from the vertex to 2 cm below the clavicle. The gross tumor volume (GTV) was defined as the respective gross extent of the tumor shown by CT/MRI after IC, including the primary tumor volume (GTVnx) and cervical lymph node tumor volume (GTVnd). A high-risk clinical target volume was defined as the nasopharynx gross tumor volume plus a 5–10 mm margin, tumor lesions before IC, and the whole nasopharynx. Low-risk clinical target volume was defined as the high-risk clinical target volume plus a 5–10 mm margin, including the skull base, clivus, sphenoid sinus, parapharyngeal space, pterygoid fossae, posterior parts of the nasal cavity, pterygopalatine fossae, retropharyngeal nodal regions, and the elective neck area from level IB to level V. Normal tissues to be contoured included the spinal cord, brain stem, temporal lobe, eyes, lens, optic nerves, chiasm, parotid glands and larynx. The total dose to the PTVg (GTV with a 0.3 cm margin) was 70–74 Gy in 33 fractions of 2.12–2.24 Gy each 5 days a week. The PTV60 (high-risk clinical target volume) covering the CTV and a 0.3 cm margin was prescribed as 60 Gy. PTV54 (low-risk clinical target volume with 0.3 cm margin) was prescribed as 54 Gy.

Chemotherapy

According to the guidelines of National Comprehensive Cancer Network (NCCN), IC plus CCRT or CCRT alone were recommended as treatment modalities for advanced NPC patients. The GP regimen was as follows: gemcitabine (1000 mg/m^2) administered intravenously for 30 min on days 1 and 8, and cisplatin (25 mg/m^2) infusion on days 1–3, repeated every 3 weeks. The TPF regimen was administered as docetaxel l60 mg/m^2 intravenously on day 1, cisplatin 20–25 mg/m^2 per day on days 1–3, and fluorouracil 600 mg/m^2 per day as a continuous 120 h infusion repeated every 3 weeks. During CCRT, chemo was planned on days 1, 22, and 43 during radiotherapy, consisting of a total dosage of cisplatin 100 mg/m^2 on day 1 or days 1–3 (cisplatin 25 mg/m^2/d) by intravenous infusion. The dose of chemotherapy agents could be feasibly modified by a 20% reduction to total withdrawal depending on the severity of chemotherapy side effects. The clinical profiles of patients who received concurrent chemotherapy were collected.

Patient assessments and follow-up

Patients were followed up by MRI of the head and neck, chest radiography or CT, and abdominal sonography every 3 months during the first 2 years, every 6 months for years 3–5 and annually thereafter. Local and regional recurrence was confirmed by nasopharyngeal biopsy and needle biopsy of a lymph node or MRI. Distant metastasis was mainly diagnosed by imaging methods such as MRI, CT or PET-CT.

Clinical endpoints

The primary endpoint is disease-free survival (DFS), defined as the time from diagnosis to the date of locoregional relapse, distant metastasis, or death from any cause, whichever occurred first. Secondary endpoints are overall survival (OS), distant metastasis-free survival (DMFS), locoregional relapse-free survival (LRFS), response rates, and toxicity profile results. OS was calculated from the date of diagnosis to death; LRFS was calculated as the date of diagnosis to first locoregional failure; and DMFS was calculated as the date of diagnosis to distant failure. Toxicity profile events encountered during the treatment were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE version 4.0).

Statistical analysis

To compare patient baseline characteristics, t-tests, chi-square tests or Fisher's exact tests were used. The DFS, OS, LRFS, and DMFS were calculated with the Kaplan–Meier method, and differences between the groups were compared by Log-rank tests. A multivariate Cox proportional hazard model was performed to evaluate the hazard ratios (HRs), 95% confidence intervals (CIs) and independent prognostic factors between different groups. The results of the main toxicities and other categorical variables were compared with the chi-square test or Fisher's exact test using SPSS IBM 22 software (SPSS Inc., Chicago, IL, USA), and MedCalc software was used for the statistical analysis. A 2-sided P value < 0.05 was considered statistically significant.

Results

Patient baseline characteristics

A total of 329 NPC patients who were treated in our hospital between December 2010 and June 2015 were reviewed. Finally, 189 (52.9%) patients were eligible for this study, including 71 in the GP group, 87 in the TPF group and 31 in the CCRT alone group. The baseline characteristics of these three groups are shown in Table 1. The gender, age, T classification, N classification, clinical stage, pretreatment level of lactate dehydrogenase (LDH), cumulative cisplatin dose

Table 1
Baseline characteristics of the 189 locally advanced NPC.

Characteristics	GP (n = 71) No. (%)	TPF (n = 87) No. (%)	CCRT (n = 31) No. (%)	*P* value[a]
Gender				0.598
Male	50 (70.4)	56 (64.4)	19 (61.3)	
Female	21 (29.6)	31 (35.6)	12 (38.7)	
Age (years)				0.225
Median (range)	48 (19–68)	45 (22–71)	45 (29–60)	
Smoking				0.535
Yes	34 (47.9)	34 (39.1)	13 (41.9)	
No	37 (52.1)	53 (60.9)	18 (58.1)	
Drinking				0.21
Yes	16 (22.5)	11 (12.6)	4 (12.9)	
No	55 (77.5)	76 (87.4)	27 (87.1)	
T category[b]				0.861
T1-2	21 (29.6)	27 (31.0)	8 (25.8)	
T3-4	50 (70.4)	60 (69.0)	23 (74.2)	
N category[b]				0.143
N1	15 (21.1)	27 (31)	12 (38.7)	
N2	41 (57.7)	38 (43.7)	16 (51.6)	
N3	15 (21.1)	22 (25.3)	3 (9.7)	
Overall stage[b]				0.403
III	24 (33.8)	31 (35.6)	7 (22.6)	
IVA	47 (66.2)	56 (64.4)	24 (68.1)	
LDH (U/L)				0.379
Median (range)	162 (94–388)	183 (97–467)	179 (124–343)	
< 245	53 (74.6)	56 (64.4)	21 (67.7)	
≥ 245	18 (25.4)	31 (35.6)	10 (32.3)	
CCD (mg/m^2)				0.468
Median (range)	408.45 (74.3–531.4)	373.49 (108.8–535.7)	300 (191.6–316.8)	
< 200	3 (4.2)	7 (8.0)	1 (3.2)	
≥ 200	68 (95.8)	80 (92.0)	30 (96.8)	
EBV-DNA (copies/mL)				0.285
< 10^3	61 (85.9)	66 (75.9)	25 (80.6)	
≥ 10^3	10 (14.1)	21 (24.1)	6 (19.4)	

Abbreviations: NPC = nasopharyngeal carcinoma; GP = cisplatin plus gemcitabine; TPF = docetaxel, cisplatin and fluorouracil; CCRT = concurrent chemoradiotherapy; LDH = lactate dehydrogenase; CCD = cumulative cisplatin dose during the whole treatment; EBV-DNA = pretreatment plasma Epstein-Barr virus deoxyribonucleic acid.

[a] P values were calculated by Chi-square test.

[b] Re-staged according to the 8th edition of UICC/AJCC staging system.

(CCD) and pretreatment level of copies of plasma Epstein-Barr virus deoxyribonucleic acid (EBV DNA) were not different among the three groups. The median follow-up time was 40 months (range: 36–52) in the GP group, 62 months (range: 41–84) in the TPF group and 63 months (range: 55–84) in the CCRT alone group. All 189 patients were followed for at least 3 years. A total of 93 patients were followed for more than 5 years, including 64 in the TPF group and 29 in the CCRT alone group. Fifty-two of the 93 patients who were followed for more than 5 years were from a phase III study that randomly assigned patients to the TPF group (n = 27) and CCRT alone group (n = 25), as these patients were from a phase III study [16].

Patient compliance and treatment response

Only 2 (2.8%) patients in GP completed one cycle, and 69 (97.2%) received 2–3 cycles of IC. In the TPF group, 82 (94.3%) patients underwent 2–3 cycles of induction chemotherapy, and just 5 (5.7%) patients completed only one cycle. There was no significant difference between the GP and TPF groups in the number of cycles of induction chemotherapy (p = 0.611). The main reasons for discontinuation were adverse events (4 of 7 patients) (57.1%) and financial problems (2 of 7 patients) (28.5%). After IC, some patients did not complete concurrent chemotherapy due to severe side effects, patient refusal or financial problems. During CCRT, 49 (69.0%) patients in the GP group, 67 (77.0%) patients in the TPF group and all patients in the CCRT alone group completed at least two cycles of concurrent chemotherapy. The most frequent reason for discontinuation of concurrent cisplatin chemotherapy in the GP group vs the TPF group was adverse events (11/22, 50.0% vs 11/20, 55.0%). All patients in the three groups completed radiotherapy as planned (Table 2). In total, 68 (95.8%) of 71 in the GP group, 80 of 87 (92.0%) in the TPF group and 30 (96.8%) of 31 in CCRT alone achieved a high level of cisplatin (≥ 200 mg/m^2).

Table 2
Treatment compliance and response to treatment.

	GP (n = 71) No. (%)	TPF (n = 87) No. (%)	CCRT (n = 31) No. (%)	*P* value[a]
Circles of IC				0.611
1	2 (2.8)	5 (5.7)	—	
2	7 (9.9)	10 (11.5)	—	
3	62 (87.3)	72 (82.8)	—	
Circles of CC				
0	11 (15.5)	9 (10.3)	0 (0)	
1	11 (15.5)	11 (12.6)	0 (0)	
2	46 (64.8)	49 (56.3)	5 (16.1)	
3	3 (4.2)	18 (20.7)	26 (83.9)	
Response to treatment (16–25 weeks after the end of radiotherapy)				0.792
CR	68 (95.8)	84 (96.6)	29 (93.5)	
PR	2 (4.2)	3 (3.4)	2 (6.5)	

Abbreviations: GP = cisplatin plus gemcitabine; TPF = docetaxel, cisplatin and fluorouracil; CCRT = concurrent chemoradiotherapy alone; IC = induction chemotherapy; CC = concurrent chemoradiotherapy; CR = complete response; PR = partial response.

[a] P values were calculated by Chi-square test.

After IMRT, 68 (95.8%) patients in the GP group, 84 (96.6%) in the TPF group and 29 (93.5%) in the CCRT alone group achieved a complete response (CR) (p = 0.79). The proportion of patients who achieved partial response (PR) was low in all three groups (3 [3.4%] in the TPF group, 3 [4.2%] in the GP group and 2 [6.5%] in the CCRT alone group), as shown in Table 2.

Long-term survival

In the present study, the 3-year survival outcome of patients was calculated in the GP group, TPF group, and CCRT alone group. As shown in Fig. 1, the 3-year DFS was 83.1% vs 81.6% vs 58.1%, the OS was 94.4% vs 92.0% vs 71%, the DMFS was 90.1% vs 90.5% vs 71.9%, and the LRFS was 94.2% vs 95.2% vs 96.6% in the GP group, TPF group, and CCRT alone group, respectively. There were no difference in the 3-year survival rate between the GP group and the TPF group. Both groups were superior to the CCRT alone group, and the disease-free survival and overall survival were significantly improved in both the GP and TPF groups.

In total, 55/189 (29.1%) patients had treatment failure, including 26/87 (29.9%) in the TPF group, 14/71 (19.7%) in the GP group and 15/31 (48.4%) in the CCRT alone group. Specifically, 15/87 (17.2%) patients in the TPF group, 6/71 (8.5%) in the GP group and 9/31 (29.0%) in the CCRT group alone developed distant metastasis; 7/87 (8.0%) in the TPF group, 6/71 (8.5%) in the GP group and 2/31 (6.5%) in the CCRT group alone group experienced locoregional recurrence. Thirteen (14.9%) patients in the TPF group, 7 (9.9%) in the GP group and 10 (32.3%) in the CCRT group alone died.

The results from the univariate analysis revealed that therapeutic modality (IC + CCRT vs CCRT alone), N stage (N1-2 vs N3) and the status of posttreatment EBV DNA (positive vs negative) are prognostic factors for OS, DFS, and DMFS; the pretreatment level of EBV DNA is a significant risk factor for OS and DFS; and a high level of cisplatin is associated with better local control. The multivariate regression analysis suggested that patients with induction chemotherapy (GP or TPF) and N1-2 had better OS, DFS, and DMFS, and pretreatment plasma EBV DNA > 10^3 copies was founded to be a significant risk factor for OS, as shown in Table 3.

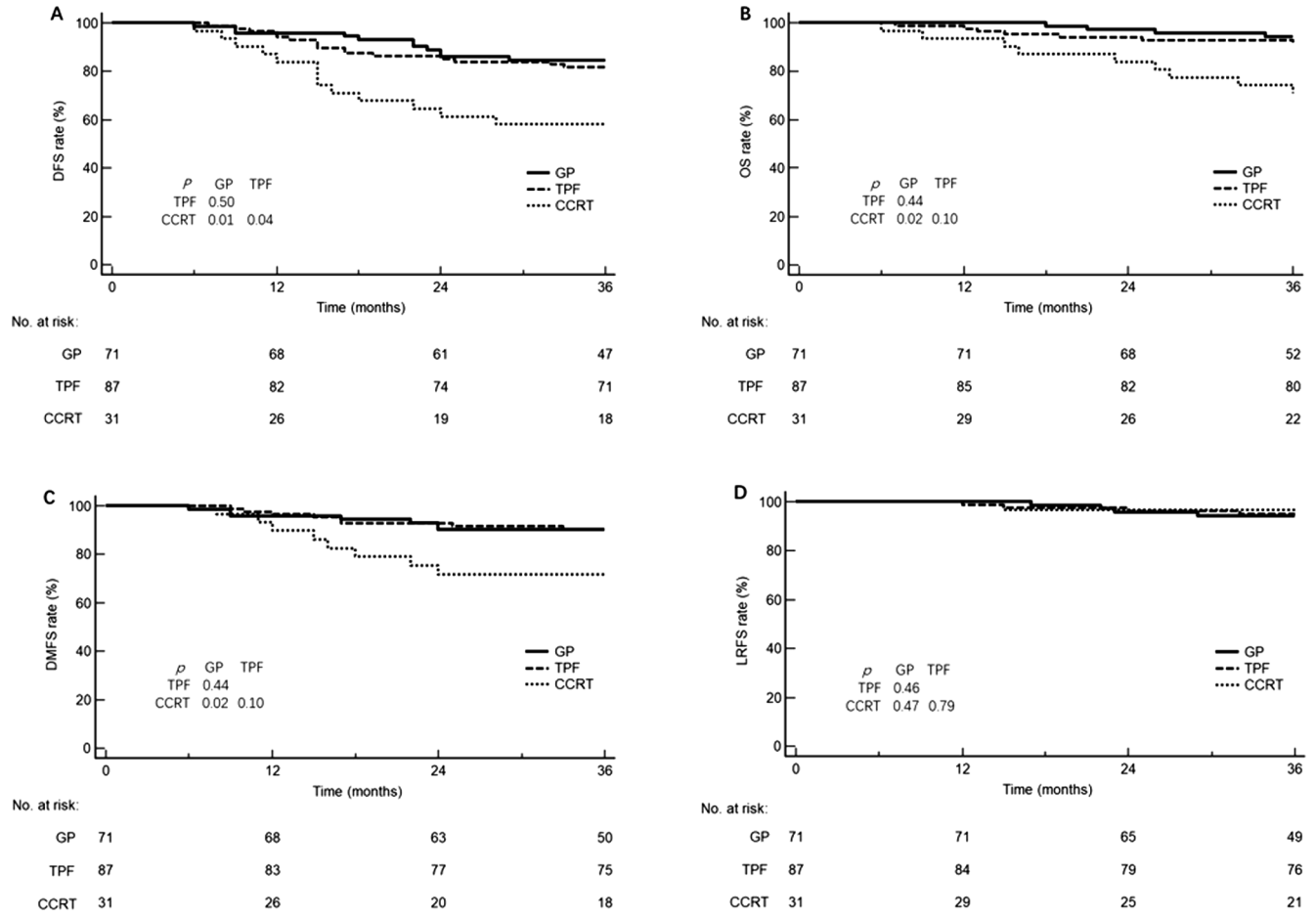

Fig. 1. Kaplan-Meier (A) disease-free survival (DFS), (B) overall survival (OS), (C) distant metastasis-free survival (DMFS), and (D) locoregional relapse-free survival (LRFS) curves for the 189 patients with locally advanced nasopharyngeal carcinoma receiving induction chemotherapy gemcitabine plus cisplatin (GP), docetaxel, cisplatin and fluorouracil (TPF), and concurrent chemoradiotherapy (CCRT) alone.

Table 3
Results of multivariate analysis for the 189 patients.

Endpoints	Variable	HR (95% CI)	*P* value[a]
DFS	N category (N1-2 vs N3)	1.84 (1.03–3.31)	0.041
	Treatment group: IC + CCRT vs CCRT	0.45 (0.24–0.81)	0.009
	EBV-DNA ($< 10^3$ vs $\geq 10^3$(copies/mL))	1.75 (0.96–3.17)	0.066
OS	N category (N1-2 vs N3)	2.28 (1.05–4.95)	0.037
	Treatment group: IC + CCRT vs CCRT	0.33 (0.15–0.72)	0.005
	EBV-DNA ($< 10^3$ vs $\geq 10^3$(copies/mL))	2.41 (1.12–5.18)	0.024
DMFS	N category (N1-2 vs N3)	2.61 (1.23–5.53)	0.012
	Treatment group: IC + CCRT vs CCRT	0.37 (0.17–0.82)	0.014
	EBV-DNA ($< 10^3$ vs $\geq 10^3$(copies/mL))	1.47 (0.62–3.83)	0.4

Abbreviations: DFS = disease free survival; OS = overall survival; DMFS = distant metastasis-free survival; HR = hazard ratio; CI = confidence interval; CCRT = concurrent chemoradiotherapy; EBV-DNA = Pretreatment Epstein-Barr virus deoxyribonucleic acid.

[a] P-values were calculated using an adjusted Cox proportional hazards model the following variables were included: N category (N3 vs. N1-2), treatment modality (IC + CCRT vs CCRT), level of pretreatment EBV-DNA($< 10^3$ vs $\geq 10^3$(copies/mL)).

Subgroup analysis

As the multivariate analysis demonstrated, N3 was a worse prognostic factor than N1-2 was for OS, DFS and DMFS. We therefore conducted a subgroup analysis to compare the two IC regimens based on the N category. In total, 121 patients who had N1-2 received IC + CCRT, with 56 in the GP group and 65 in the TPF group. As shown in Fig. 2A–C, the 3-year DFS, OS, and DMFS rates for the GP vs TPF regimens were 87.5% vs 87.7% (p = 0.78), 96.4% vs 95.4% (p = 0.70) and 94.6% vs 90.7% (p = 0.24), respectively. In the 37 patients who had N3 disease, 15 patients received GP induction chemotherapy, while 22 patients received TPF. The 3-year DFS, OS, and DMFS rates were 73.3% vs 63.6% (p = 0.29), 86.7% vs 81.8% (p = 0.75) and 73.3% vs 90.5% (p = 0.77) for the GP vs TPF regimens, respectively (Fig. 2D–F). These findings indicated that GP can achieve similar outcomes as TPF even in patients with a significantly greater burden and higher risks of death or distant metastasis.

We also performed a subgroup analysis in 150 patients who had detectable EBV DNA before treatment. Of these patients, 52 were from GP group, 77 from TPF group, and 21 from CCRT alone group. In this group of patients, those with negative EBV DNA after treatment had a relatively better prognosis (supplement Fig). EBV DNA in 35 of 52 patients from GP group (67.3%) and 40 of 77 patients from TPF (51.9%) had become negative after treatment. There was no difference between two IC regimens in negative posttreatment EBV DNA (supplement table).

Acute toxicity

During induction chemotherapy, the most common grade 3–4 adverse effect was leucopenia, which occurred significantly more often in TPF group than in GP group (25/87 [28.7%] vs 8/71 [11.3%], p = 0.007). There was also significantly more neutropenia in TPF group than in GP group (18/87 [20.7%] vs 6/71 [8.5%], p = 0.033). Between

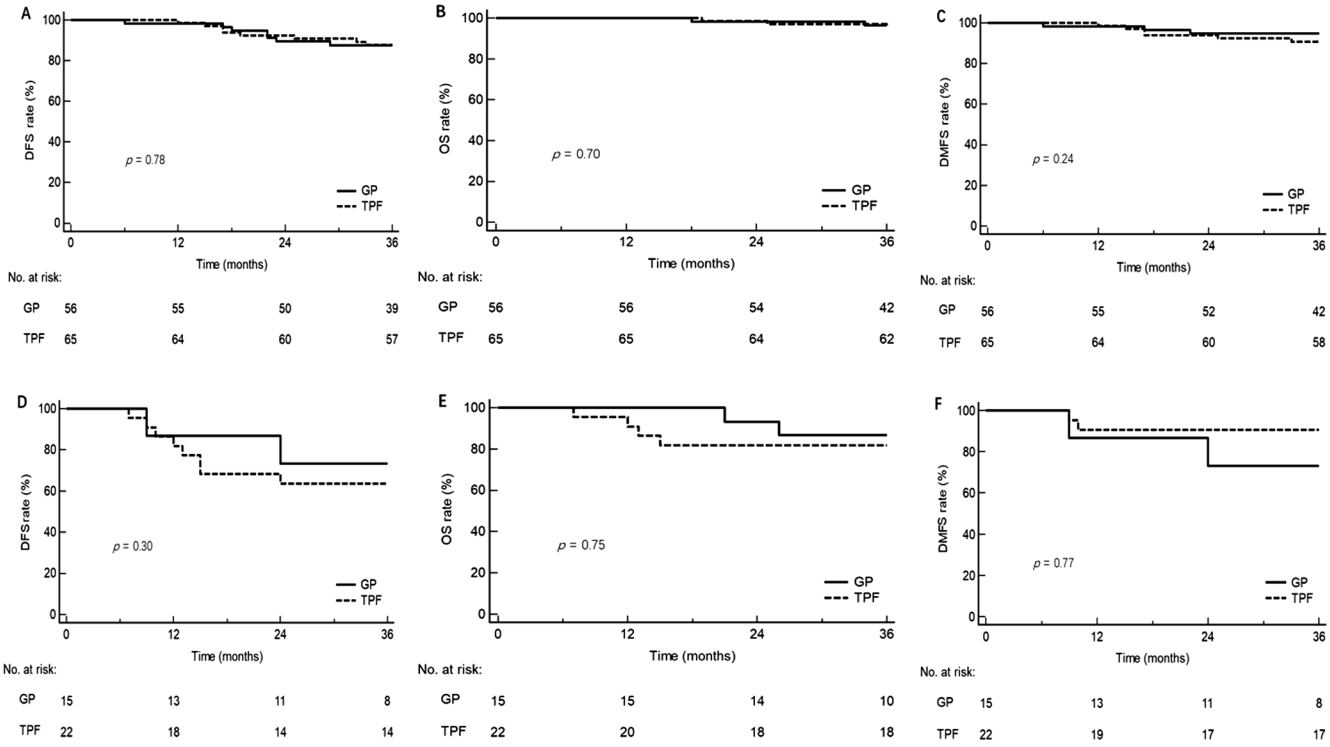

Fig. 2. Kaplan-Meier disease-free survival (DFS), overall survival (OS) and distant metastasis-free survival (DMFS) curves for the 121 patients with N1-2 (a) and 37 patients with N3 (b) received induction chemotherapy of cisplatin plus gemcitabine (GP) and docetaxel, cisplatin and fluorouracil (TPF).

Table 4
Grade 3–4 acute toxicities during IC and treatment among the three groups.

Grade 3–4 toxicities	GP (n = 71)	TPF (n = 87)	CCRT (n = 31)	*P* value[a]
	No. (%)	No. (%)	No. (%)	
During IC				
Leucopenia	8 (11.3)	25 (28.7)	—	0.007
Neutropenia	6 (8.5)	18 (20.7)	—	0.033
Anaemia	1 (1.4)	2 (2.3)	—	0.576
Thrombocytopenia	5 (7.0)	1 (1.1)	—	0.091
Nausea	3 (4.2)	3 (3.4)	—	0.8
Vomiting	10 (14.1)	12 (13.8)	—	0.958
Mucositis	0 (0)	1 (1.1)	—	0.274
Liver	1 (1.4)	1 (1.4)	—	0.885
Rash	2 (2.8)	2 (2.3)	—	0.837
Diarrhoea	0 (0)	1 (1.1)	—	0.274
During treatment				
Leucopenia	10 (14.1)	30 (34.5)	6 (19.4)	0.009
Neutropenia	10 (14.1)	21 (24.1)	1 (3.2)	0.021
Anaemia	1 (1.4)	2 (2.3)	0 (0)	0.524
Thrombocytopenia	5 (7.0)	1 (1.1)	1 (3.2)	0.139
Nausea	5 (7.0)	6 (6.9)	1 (3.2)	0.7
Vomiting	10 (14.1)	15 (17.2)	2 (6.5)	0.289
Mucositis	10 (14.1)	15 (17.2)	3 (9.7)	0.564
Liver	1 (1.4)	2 (2.3)	0 (0)	0.524
Rash	2 (2.8)	2 (2.3)	0 (0)	0.393
Diarrhoea	1 (1.4)	2 (2.3)	0 (0)	0.524

Abbreviations: GP = cisplatin plus gemcitabine; TPF = docetaxel, cisplatin and fluorouracil; CCRT = concurrent chemoradiotherapy alone.

[a] P-values were calculated by Chi-square test or Fisher exact test.

the two IC groups (6/71 [8.5%] vs 18/87 [20.7%], p = 0.033). During the CCRT course, grade 3 or 4 leucopenia occurred most across these three groups (GP vs TPF vs CCRT are 10/71 [14.1%] vs 30/87 [34.5%] vs 6/31 [19.4%], p = 0.009), followed by neutropenia (14.1% vs 24.1% vs 3.2%, p = 0.021), vomiting (14.1% vs 17.2% vs 6.5%, p = 0.289), and stomatitis (mucositis) (14.1% vs 17.2% vs 9.7%, p = 0.564), as shown in Table 4.

Discussion

Distant metastasis remains a major issue in the treatment of locally advanced NPC, which has obtained a satisfactory local regional control with the application of IMRT and a combination of chemoradiotherapy. Although concurrent chemotherapy improves treatment outcomes in patients with locally advanced NPC, the distant metastasis rate remains high. Adding adjuvant chemotherapy or induction chemotherapy may contribute to a better control. However, a phase III trial and its long-term results have found that adjuvant cisplatin and fluorouracil chemotherapy failed to obtain survival benefit [13,14]. In addition, another study has shown that, even for patients with positive posttreatment plasma Epstein-Barr virus (EBV) DNA, which is a high-risk factor, adjuvant chemotherapy still did not improve survival outcomes [29]. In contrast, induction chemotherapy has been effective in several phase III trials [15–18]. As induction chemotherapy plus concurrent chemoradiation has been validated as an effective treatment regimen, more effective induction chemotherapy regimens with less side effects are needed.

Currently, induction chemotherapy regimens for locally advanced NPC include TPF, TP, PF, and GP. Studies have already found that TPF is superior to PF and TP [19–21]. However, the incidence of grade 3–4 adverse reactions, especially leucopenia and neutropenia, are higher in patients receiving 2–3 cycles of TPF chemotherapy. The central venous catheter (CVC) device for intravenous infusion of docetaxel is inconvenient. For patients with hypertension, diabetes or other endocrine system diseases, pretreatment with glucocorticoids may increase their risk of side effects. Therefore, other alternative regimens must be explored. A multicenter, randomized study has shown that gemcitabine plus cisplatin (GP) results in better survival than PF in patients with recurrent or metastatic NPC [23]. In addition, studies from a phase III clinical trial and some phase II studies have indicated that GP is also be effective in locally advanced NPC [24,26–28]. However, in clinical practice, the best choice for an induction chemotherapy regimen for patients with locally advanced NPC remains to be determined.

In the present study, the CCRT alone regimen was included to further confirm the validity of GP as an induction chemotherapy regimen and to test the long-term effects of the TPF regimen. In the present study, the efficacy of the GP and TPF regimens in induction chemotherapy for locally advanced nasopharyngeal carcinoma was better than that of concurrent chemoradiotherapy alone, and the efficacy was comparable between GP and TPF. The incidence of 3–4 grade toxic reactions with the GP regimen was lower than that with the TPF regimen. Our results showed that there is no difference between the two IC regimens of TPF and GP in 3-year survival rates, consistent with previous results from our center [30]. Compared with CCRT alone, the addition of GP induction chemotherapy improved the 3-year DFS, OS, and DMFS rates of patients with stage III-IVA NPC. Compared with other reported studies on GP-based IC before CCRT or RT alone, patients in our study achieved similar survival outcomes, with a 3-year DFS of 83.1%, OS of 94.4%, DMFS of 90.1%, and LRFS of 94.2% [24–28].

The DFS, OS, and DMFS rates of the concurrent chemoradiotherapy alone group in our study were lower than those in previous trials using IMRT [15–18,28]. The reasons for these differences are as follows. In the CCRT group, 25/31 (80.64%) patients were from a phase III study [16]. As the study demonstrated, IC plus CCRT can significantly increase the survival outcome of patients with locally advanced NPC. These patients should have received IC + CCRT, but they only received CCRT alone. Furthermore, the ratio of patients with stage IVA disease was much higher in this group. However, our study found that there was no significant difference in the DMFS rate between the TPF group and the CCRT alone group, contradicting the findings of a previous study [16]. The explanation could be that, compared with previous studies, the TPF group in our study contained more patients with N3, which is a high-risk factor for distant metastasis.

First, we found that compared with N1-2, N3 was an independent prognostic factor for locally advanced NPC. Patients with N3 had worse survival outcomes than those with N1-2, consistent with published studies [31,32]. Theoretically, three-drug combinations may be more effective than two-drug combinations. Therefore, we performed a subgroup analysis to compare the two regimens for patients with different metastasis risks. In patients with N1-2 or higher distant metastasis risk, such as N3, there was no significant difference between the two regimens in survival outcomes. Our study suggests that even for patients with locally advanced NPC who are at high risk of metastasis, the GP regimen is no less effective than the TPF regimen. Second, multivariate regression analysis also indicated that high levels of pretreatment EBV DNA ($> 10^3$ copies/ml) were associated with worse OS and DFS (with a marginally significant difference [P = 0.066]). The univariate analysis also showed that patients with positive detection of posttreatment EBV DNA also have a relatively worse DFS, OS and DMFS, which has been proven in previous studies [33,34]. Further comparisons showed that there is still no difference between the two regimens in patients with positive detection of EBV DNA.

Apparently, the three-drug combination induction chemotherapy regimen resulted in more grade 3–4 treatment-related toxic events than the two-drug combination regimen did. Comparison between the two regimens suggested that the TPF group produced more grade 3–4 toxicities, mainly hematological, than GP or CCRT alone. The incidence rate of grade 3–4 hematological toxic events in the TPF group was similar to the findings in previous reported studies, whereas the CCRT alone group had relatively fewer events [16,21].

Conclusion

Our study found that the GP induction regimen achieved equivalent efficacy compared to the TPF induction regimen, and the incidence of grade 3–4 hematological toxic events was relatively lower with GP than with TPF. Prospective and large sample studies are awaited to validate our conclusion.

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

None declared.

Acknowledgement

We sincerely thanked Mr. Zhe Liu for providing patients' data, and Dr. Ping Zhu for providing the support in statistical analysis.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.08.001.

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